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Pregnancy outcomes following exposure to abatacept during pregnancy

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ABSTRACT

Objective: To characterize pregnancy outcomes following maternal and paternal exposure to abatacept, using clinical trial and post-marketing data available to the manufacturer.
Methods: All confirmed cases of pregnancy with outcome data reported to the manufacturer up to September 1, 2014 were included. Sources included clinical trials, spontaneously reported (unsolicited) post-marketing cases, and the Organization of Teratology Information Specialists registry. Details recorded included number of live births, spontaneous abortions and terminations, pregnancy complications, and congenital anomalies.
Results: A total of 161 pregnancies with known outcomes were identified between 1995 and September 2014: 151 were following maternal exposure to abatacept and 10 were following paternal exposure. Seven of 86 (8.1%) live births following maternal exposure had congenital anomalies (cleft lip/cleft palate, congenital aortic anomaly, meningocele, pyloric stenosis, skull malformation, ventricular septal defect/congenital arterial malformation, and Down's syndrome with premature rupture of membranes at 17 weeks that resulted in a live birth via cesarean section and subsequent infant death). In addition, 59 of the 151 (39.0%) cases with maternal exposure resulted in abortions (40 spontaneous and 19 elective). Of the 10 pregnancies with paternal exposure, there were nine live births and one elective abortion, with no congenital abnormalities identified and no fetal deaths.
Conclusions: Based on these data, there does not appear to be a pattern of congenital anomalies following maternal or paternal exposure to abatacept. No cases of vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, or limb abnormalities (VACTERL) were noted. Spontaneous abortion rates were within expected range. Abatacept should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Introduction

Inadvertent exposure to medications during pregnancy is of concern to both patients and their healthcare providers, particularly since approximately 50% of pregnancies are unplanned [1]. This is an especially important issue for women taking medications to manage chronic conditions such as autoimmune diseases. Autoimmune diseases such as rheumatoid arthritis (RA) disproportionately affect women, including those of childbearing potential. Non-biologic and biologic disease-modifying antirheumatic drugs (DMARDs) that are used to treat these diseases act by directly modifying immunological pathways involved in the disease pathology [2–4]. Unintentional exposure to these drugs may easily occur in cases of unplanned pregnancy, and patients and rheumatologists need information regarding the use of drugs during pregnancy and lactation. Some drugs can cross the placenta, depending on the treatment and trimester [4–9]. On the other hand, uncontrolled inflammation adversely affecting the mother, such as that caused by RA, will create a hostile environment for the fetus [5,10]. In addition, patients with higher RA disease activity are at an increased risk of pregnancy loss, preterm labor, and low birth-weight babies [5,9–11]. The physician and pregnant patient must balance the potential benefits of DMARDs

Abbreviations: DMARD, disease-modifying antirheumatic drug; FDA, Food and Drug Administration; MADCF, Metropolitan Atlanta Congenital Defects Program; MMF, mycophenolate mofetil; MMS, mycophenolate sodium; MTX, methotrexate; OTIS, Organization of Teratology Information Specialists; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor.

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Competing interests: Laura Ray, Sudha Vemuri, and Teresa A. Simon are employees and stockholders of Bristol-Myers Squibb. Monica Kumar is a former employee and stockholder of Bristol-Myers Squibb and currently an employee of Sanofi US.
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against the risks these medications may pose to the developing fetus, using all available nonclinical and clinical data to make an informed decision.

There is limited information on exposure to DMARDs during conception, pregnancy, and lactation [5,6,12]. To help differentiate potential risk, the US Food and Drug Administration (FDA) previously classified medications into five pregnancy categories (A–D, X, with a separate designation N for those medications that are not categorized) based on available nonclinical and clinical data to indicate the potential of a drug to cause birth defects if used during pregnancy [13]. However, since this classification system has acknowledged imperfections, the FDA has released new guidance regarding labeling of products with regard to use during pregnancy and lactation. These labeling changes are designed to help improve the communication of this benefit–risk assessment. Beginning in June 2015, the five pregnancy categories will no longer be used; all newly approved drugs and biologic products will adhere to the new labeling rule, which will include a summary of the risks of using a drug during pregnancy and lactation, a discussion of the supporting data, and information to help healthcare providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation [14]. The new labeling will be phased in gradually for currently approved drugs and biologic products.

Most of the current knowledge regarding the safety of DMARD use during pregnancy is based on observations from unplanned pregnancies while receiving the drug [5,7,15]. Based on currently available evidence, DMARDs have been classified into several different FDA categories. For example, the non-biological DMARDs methotrexate (MTX) and leflunomide (both FDA category X) are known to cause fetal death or teratogenic effects and must be withdrawn prior to planned pregnancy [8,16]. Mycophenolate mofetil (MMF) or mycophenolate sodium (MMS) (FDA category D) are associated with increased risk of congenital anomalies and pregnancy loss in the first trimester [17–19]. On the other hand, the biologic DMARDs including tumor necrosis factor (TNF) inhibitors such as adalimumab, etanercept, certolizumab pegol, golimumab, and infliximab (all FDA category B), have no recorded teratogenic effects in animal studies but are still lacking adequate human pregnancy safety data. Observational studies have shown that 12–20% of patients with RA receive TNF-inhibitor therapy throughout pregnancy [6,20]. Data from these studies have shown no increase in the risk of adverse pregnancy or fetal outcomes from exposure to TNF inhibitors in pregnancy [4,5,7,21,22], although there is insufficient evidence to prove absolute safety [23]. Limited clinical data are available on the use of other biologic DMARDs, including rituximab (FDA category C), anakinra (B), tocilizumab (C), and abatacept (C), during pregnancy [4–7,22,24,25].

Abatacept is a selective T-cell costimulation modulator approved in multiple countries for the treatment of RA. It is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4 linked to the modified Fc portion of human immunoglobulin G1. In animal studies, abatacept crossed the placenta (maternal sera concentrations 1.7–2.4 times higher than fetal sera concentrations) but was not found to be teratogenic in mice, rats, or rabbits at approximately 29 times exposure associated with maximum recommended human dose ([26] and data on file). However, only limited data are available regarding pregnancy outcomes in humans treated with abatacept [24]. As there are no adequate and well-controlled studies of abatacept use in pregnant women, the prescribing information states that abatacept should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus [26].

In this report, we present a descriptive analysis of known pregnancy outcomes following maternal and paternal exposure to abatacept, using clinical trial, spontaneous post-marketing reports, and registry data.

Methods

Patient population included in the analysis

Pregnancy outcomes were evaluated in female or male patients exposed to abatacept. All medically confirmed cases of pregnancy with outcome data reported to the manufacturer from initial phase 1 studies commenced in 1995 to September 1, 2014 were included in the study.

In the randomized controlled trials (RCTs), all patients were required to have been on a background DMARD regimen (54% received MTX). Women of childbearing potential enrolled in the clinical trials had to undergo a pregnancy test at every visit prior to abatacept treatment; thus, there were monthly pregnancy tests during the blinded phase of the studies. Moreover, women of childbearing potential who were unwilling or unable to use an acceptable method of contraception for the entire study period and for up to 10 weeks after the last dose of investigational product were excluded from the trials, as were women who were pregnant or breastfeeding and those with a positive pregnancy test result on enrollment or before administration of an investigational drug. Patients found to be pregnant during the study were withdrawn from the trial and abatacept was discontinued.

Data collection

Data on pregnancy outcomes following maternal or paternal exposure were obtained from the Bristol-Myers Squibb safety database that includes clinical trial data (prospective) and post-marketing reports (prospective and retrospective data). The safety database was searched for all reports of pregnancy from 1995 to 2014. Post-marketing data were obtained from spontaneous case reports submitted to the relevant regulatory health authorities, direct reporting of exposure from individuals and healthcare providers, phase 4 studies, and the Organization of Teratology Information Specialists (OTIS) registry (ongoing autoimmune diseases in pregnancy study, http://www.pregnancystudies.org/ongoing-pregnancy-studies/autoimmune-studies/). OTIS collects health information from women who take medicines or vaccines during pregnancy, and provides evidence-based information to healthcare professionals and the general public about medications and other exposures during pregnancy and breastfeeding. Participants were enrolled after contacting OTIS and subsequently interviewed and asked about their health history, pregnancy, and the birth. The OTIS study is approved by the Institutional Review Board of the University of California, San Diego.

Details recorded included the number of live births, spontaneous abortions, and terminations. In addition, details of pregnancy complications and of any congenital abnormalities were recorded. Congenital anomalies were identified using the Centers for Disease Control and Prevention's Metropolitan Atlanta Congenital Defects Program (MACDP; version 08/07; http://www.cdc.gov/ncbddd/birthdefects/MACDP.html), which is a population-based active surveillance system for birth defects. For pregnancy cases from clinical trials, follow-up was as follows: two attempts for initial reports of pregnancy, three attempts to obtain outcome, and two additional attempts for follow-up as appropriate.

Results

Patient demographics and distribution of cases

A total of 161 discrete pregnancies with known outcomes were identified; 100 cases were reported before the outcome occurred (prospectively) and the remaining 61 were reported after the outcome occurred (retrospectively). Maternal exposure to abatacept occurred in 151 cases and 10 cases were following paternal exposure.

For both clinical trials and spontaneous post-marketing case reports, approximately 50% of cases were reported from the USA, Mexico, Canada, or Argentina. All other cases were reported from South America, Europe, South Africa, or East Asia.

Maternal exposures

Of the 151 maternal exposure pregnancies with known outcomes, 68 were from the clinical trials, 80 were reported as post-marketing reports, and three were from the ongoing OTIS registry. The mean (range) maternal age of patients in the clinical trials was 30.1 (15–44) years, and 31.2 years in post-marketing/spontaneous case reports. Relevant medical history and concomitant medications are presented in Table 1.

Pregnancy outcomes

The outcomes of pregnancies with maternal exposure ($n = 151$) to abatacept overall and stratified by clinical trials and post-marketing reports are reported in Table 2. Seven MACDP-identified congenital anomalies were recorded among the 86 live births; one of the seven was Down's syndrome that resulted in infant death at birth following a premature rupture of membranes. Overall, 40 spontaneous abortions, including a late abortion at approximately 21 weeks of gestation, occurred and 19 elective terminations were performed.

Reported anomalies

The identified congenital anomalies included cleft lip/cleft palate, congenital aortic anomaly, meningocele, pyloric stenosis, skull malformation, ventricular septal defect/congenital arterial malformation, and Down's syndrome with premature rupture of membranes at 17 weeks that resulted in a live birth via cesarean section and subsequent infant death. Reported anomalies were identified from OTIS (3/7) and post-marketing/unprompted reports (4/7); no anomalies were seen in the live births that occurred in the clinical trials. Pregnancy details and maternal medical histories for the congenital anomalies reported in the OTIS registry and post-marketing reports are detailed in Table 3. Most of the exposures associated with congenital anomalies occurred in the first trimester and were reported in patients who took concomitant medications of category D or X, including leflunomide, MTX, MMF, and MMS. Table 2 summarizes the details for abortions and fetal deaths that occurred following maternal exposure to abatacept; the majority of spontaneous abortions in the clinical trials (13 out of 17) occurred within the first 10 weeks. Notably, 20/40 of all patients (50%) who experienced spontaneous abortions received concomitant MTX, including 12/17 patients (70.6%) in the clinical trials.

Table 1
Maternal demographic characteristics in pregnancies with known outcomes

Patient characteristic[a]	RCT	Post-marketing and spontaneous case reports	OTIS registry
n	68	80	3
Mean age, years	30.1	31.2	32.7
History of diabetes, *n*			
Pre-gestational	1	3	1
Gestational	4	1	–
Drug discontinuation, %	100	100	100

OTIS, Organization of Teratology Information Specialists; RCT, randomized controlled trial.

[a] For cases where information was available.

Fetal deaths

Four of the pregnancies resulted in fetal death, with limited information available. Details available on the four cases are listed below: (1) intrauterine fetal death due to an unknown cause occurred at approximately 24 weeks of gestation and the pregnancy was terminated via cesarean section, (2) during the pregnancy with diagnosed Down's syndrome, the patient experienced a premature rupture of membranes at 17 weeks of gestation that resulted in a live birth via cesarean section and subsequent infant death, (3) death occurred at or shortly after delivery (at term) following a grade IV hemorrhagic stroke, and (4) the final case of fetal death occurred at approximately 15 weeks of gestation and was possibly related to maternal toxoplasmosis.

Postnatal follow-up

Postnatal follow-up to 1 year was available for 16 cases in the RCTs. Length of follow-up ranged from 6 to 49 weeks. None of the infants for whom postnatal follow-up was available were diagnosed with anomalies after birth, and no immune deficiencies were reported.

Paternal exposures

Of the 10 pregnancies with paternal exposure to abatacept, there were nine live births and one elective abortion, with no congenital abnormalities identified and no fetal deaths (data not shown). Six of the cases were reported prospectively and four were retrospective. Among the nine live births following paternal exposure, reported concomitant medications of category D or above were MTX ($n = 3$), leflunomide ($n = 1$), and MMF/MMS ($n = 1$).

Discussion

Pregnancy alters autoimmune disease pathophysiology and drug metabolism, and both the disease and its treatment can have unpredictable effects on the unborn child [5]. Studies to date have shown no increased risk of adverse pregnancy or fetal outcomes from exposure to TNF inhibitors during pregnancy [4,5,7,21,22]; however, there is a paucity of data available on use of other biologic DMARDs during pregnancy [4–7,22,24,25].

Here, we report for the first time pregnancy outcomes with abatacept exposure. A total of 161 pregnancies with known outcomes were identified, including 151 with maternal exposure to abatacept and 10 with paternal exposure. In the 86 live births following maternal abatacept exposure, seven (8.1%) MACDP-identified congenital anomalies were recorded. No cases of vertebral defects, anal atresia, cardiac defects, tracheo-esophageal

Table 2
Overview of pregnancy outcomes with maternal exposure to abatacept

Outcomes	Count, n	RCT	Post-marketing and unprompted case reports	OTIS registry
	N = 151	*n* = 68	*n* = 80	*n* = 3
Total live births, n (%)	86 (60.0)	35 (51.5)	48 (60.0)	3 (100)
Congenital anomalies[a], *n (%)*	7 (8.1)	–	4 (5.0)	3 (100)
Cleft lip/cleft palate	1	–	–	1
Down's syndrome	1	–	1	–
Congenital aortic anomaly	1	–	1	–
Meningocele	1	–	1	–
Pyloric stenosis	1	–	–	1
Skull malformation	1	–	1	–
Ventricular septal defect; congenital arterial malformation	1	–	–	1
Abortion, n				
Spontaneous, *n* (%)	40 (26.5)	17 (25.0)	23 (29.0)	
Age, mean (range), years[b]	31.9 (17–44)	32.9 (20–44)	31.1 (17–41)	
Concomitant methotrexate, *n*[b]	20	12	8	
Timing, *n*[b]				
≤ 10 weeks	15	–	2	
≤ 6 weeks	9	9	–	
7–10 weeks	4	4	–	
First trimester[c]	6	2	4	
Unknown	19	2	17	
Type 1 diabetes, *n*	1	–	1	
Elective, *n* (%)	18 (12.0)	12 (17.6)	6 (7.5)	
Late	1	1	–	
Fetal death, n (%)[d]	4	2	2	–

OTIS, Organization of Teratology Information Specialists; RCT, randomized controlled trial.

[a] Six of the seven are included in the live births category.
[b] Where information was available.
[c] Exact date not provided.
[d] Fetal death was defined as intrauterine death of a fetus > 20 weeks of gestation.

fistula, renal anomalies, or limb abnormalities (VACTERL) were noted. The available data for abatacept presented here do not appear to show a pattern of congenital anomalies following maternal or paternal exposure. In addition, 59 of the 151 pregnancies resulted in abortions (40 spontaneous and 19 elective). Where data were available regarding concomitant medications, MTX was the most common reported agent.

The management of patients with RA wishing to conceive involves adaptation of treatment to keep disease controlled, but pregnant women should not receive teratogenic drugs such as

Table 3
Pregnancy details for the observed congenital abnormalities

Observed congenital anomalies	Number, *n*	Retrospectively reported	Maternal age, years	Maternal race	Time of exposure	Exposure to concomitant medications[a]	Maternal medical history	Country
OTIS registry								
Cleft lip/cleft palate	1	Y	36	Black	First trimester	–	Type 2 diabetes	USA
Pyloric stenosis	1	Y	25	White	First trimester	–	Hypertension, depression/ anxiety, fibromyalgia, and hypothyroidism	USA
Ventricular septal defect and congenital arterial malformation	1	Y	37	Unknown	First trimester	Leflunomide	Hypothyroidism	USA
Post-marketing and unprompted case reports								
Down's syndrome[b]	1	Y	28	Unknown	Unknown	–	n/a	Argentina
Congenital aortic anomaly	1	N	27	White	First trimester	–	Type 1 diabetes	USA
Meningocele	1	Y	Unknown	Unknown	Unknown	Mycophenolate mofetil Mycophenolate sodium	n/a	France
Skull malformation	1	N	31	White	First trimester	–	n/a	Belgium

FDA, Food and Drug Administration; n/a, not available; OTIS, Organization of Teratology Information Specialists.

[a] Only concomitant medications that are FDA pregnancy category D or higher in the USA are listed.
[b] Resulted in fetal death.

MTX [9]. RA must be controlled while patients are attempting to conceive, and time to conception is longer in those with higher disease activity [27]. In addition, patients with RA are more likely to have preterm births [28]. Elevated disease activity during pregnancy is associated with rapid postnatal catch-up growth in offspring, a risk factor for cardiovascular disease in adulthood [29]. In patients treated with MTX, pregnancy losses of approximately 42% are seen, with twice as many birth defects noted compared with non-treated patients [30]. Verstappen et al. [31] reported that the rate of spontaneous abortion was highest (27%) in patients exposed to anti-TNFs during pregnancy at the time of conception. The rate of spontaneous abortion in our data set was 25.8% overall and similar to the published rate of spontaneous abortions, if clinically undetectable pregnancies are included [31,32]. Half of the patients who experienced spontaneous abortions received concomitant MTX. Furthermore, the incidence of early miscarriage is unknown for women with autoimmune diseases [31]. In addition, the increased rate of spontaneous abortions observed may in part be due to detection bias: clinical trials are closely monitored and approximately 50% of the spontaneous abortions identified in the RCT data were identified early (<6 weeks) and may not have been identified or clinically detected if the patients had not been enrolled in a clinical trial.

This study reports data from a small number of patients with maternal pregnancy outcomes, of which 45% were obtained from post-marketing and spontaneous sources. Although those sources are effective and valuable in capturing data, there are many limitations of the data that may make them difficult to interpret and limit the ability to generalize them. The treated patients in these reports may have had greater disease severity, comorbidities may have been unknown, no denominator for comparison was available, and data were often recorded incompletely and/or inconsistently [5]. In addition, the data were mostly retrospective, which usually are negatively biased and subject to recall with limited follow-up. These study limitations and the effect of RA on pregnancy may account for the number of MACDP-identified congenital anomalies (8.1%) being slightly greater that that seen in the general population (3–5%).

Bristol-Myers Squibb continues to monitor and collect information on the outcomes of abatacept-exposed pregnancies in an ongoing study using the OTIS Research Group as an integrated project within the existing OTIS Autoimmune Diseases in Pregnancy Project [33]. This prospective, observational, cohort study of women exposed to abatacept will continue data collection for the next several years. However, the long-term effects of abatacept on the developing immune system are presently not known and abatacept should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Therefore, patients of childbearing potential with RA who are being treated with DMARDs require counseling with regard to pregnancy outcomes [6,34].

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